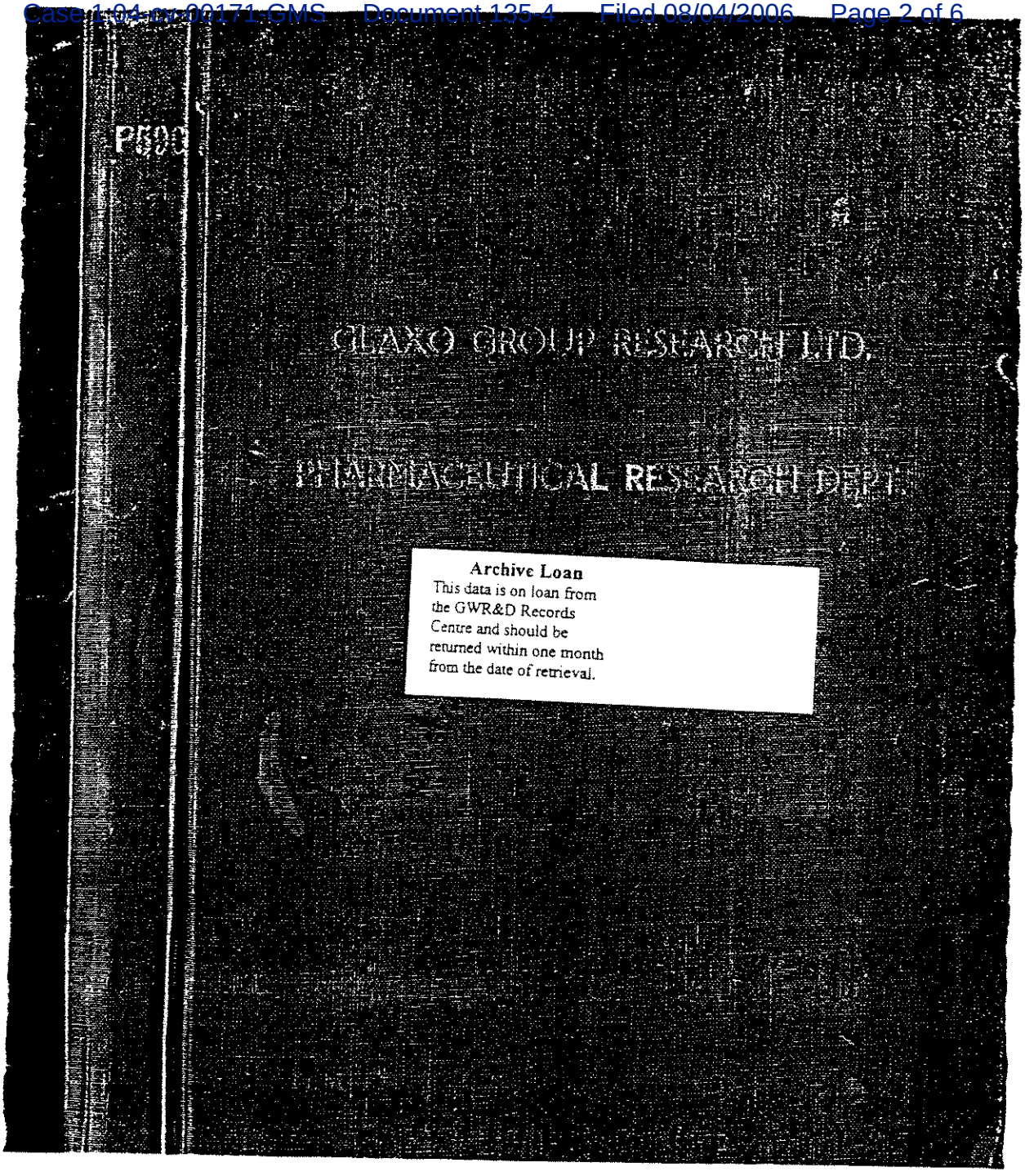

PLAINTIFF'S TRIAL EXHIBIT 238

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Y084309

14 25/7/83 S.W.

Summary of Present Situation:

The following strategy is being ~~progressed~~ adopted:-

1 Other manufacturers sugar-free syrups. ..... (from PI ... 29.5.83)

Assessing the ability of sugar-free syrups of other manufacturers to prevent proliferation of Ps. cepacia. If few or none could cope with this contamination, decision must be made, whether it is acceptable to launch Zantac syrup on the basis of "everybody else has the same problem". See page 3 for details.

2 Interim Solution

Challenge the syrup proposed for marketing with Ps. cepacia (cultivated in Zantac Syrup) and store at 4°. If these results prove satisfactory could launch in UK with 4° storage in-use. A reformulated product would be introduced ASAP.

For the USA a decision is required. a) 4° storage acceptable?
b) wait for reformulation?
c) go for creamer pack only with the formulation having most supporting data ie propyl/butyl only

3 Resurrect the Original Formulation.

Challenge the syrup containing methyl, propyl and butyl parabens (after 27+/12m storage ≡ 30°/5yr), with Ps. cepacia at room temp. If results satisfactory, get analysis done and submit another P.L. application. For the USA, new stability programmes will have to be set up to cover PET.

4 Minor Reformulation.

4.1. Use the same bottle: as in 2, but include 5% w/v EtOH and challenge with Ps cepacia. If this is satisfactory (and 1,2,3 are not) then:-

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(a) check acceptability of EtOH inclusion 2

(b) check syrup acceptable in all other respects, as well as USP/BP challenge.

(c) Put up more UK stability batches for PL / USA for NDA.

4.2 Repeat 4.1 with 2.5% w/v propylene glycol.

4.3 Repeat 4.1 with 0.1% w/v phenol.

Submissions for 4.1, 4.2, 4.3 would probably need to be self-supporting

Pros and Cons of Propylene Glycol + Ethanol

Acceptable daily intake	25mg/kg	Lower.
For 20kg subject	500mg	
Acceptable conc in 20ml syrup.	2.5% w/v	
Anti-microbial activity.	mould growth inhib similar →	
Medical acceptability		
Stability of ranitidine	Presumed OK from flavour	Probably OK.
Tame prod manufacture	though high flash point.	14° flash point.
Volatility glass/PET.		
Facilitates manufacture to dissolve parabens.	✓	✓
Density	1.04	0.8
B.P.	185-189	78°
Taste (neat)	slightly sweet.	burning taste.

MS 25/7/85 5.2

5 Major Reformulation? - No dates fixed - costs?

In addition to the in-use contamination problem, there are other less-than-perfect properties of the syrup:-

- string development on storage.
- flavour per se.
- mint flavour haze (at 0.5% w/v).
- parabens hydrolysis enhanced by ionic conc.

These aspects should be considered at reformulation.

5.1 Preservative * lit. search in hand (complete 2/8/85)

Possible:- 5% Ethanol* USP/BP
2.5% Propylene Glycol (in favour) USP/BP
0.1% Phenol*
combined with parabens.
Ethylhydroxybenzoate USNF
Phenylethyl alcohol* USP/BP
Phenoxyethyl alcohol* USP/BP
Phenoxyethanol* B.P. only
Bronopol
50% Sucrose USP/B.P.
Benzalkonium Chloride USP/BP
Unit dose

} Antimicrobial action
- Precedents
- Medical acceptability
- Stability of ranitidine
- Stability of preservative
- ok in Pet
- Cellulose compatibility
- Clarity.

Unsatisfactory

Chlorbutol - 25°/pH7/ 1/2 life 0.2yr. (Martindale).
Benzoic acid - ineffective pH > 5.
Sorbic acid - "
Phenylmercurics - Hg.

5.2 Ionic strength

Reduce to reduce parabens hydrolysis (phosphates and NaCl).

5.3. HPMC

Omit or change conc or change grade. Sucrose?

5.4 Sorbitol.

Please conc. to Kirken, Sucrose? Diarrhoea? Lycasin?

5.5 Flavour.

~~Increase conc~~ Humble flavour but at least compatible with ranitidine. Could be a lot of work. Saccharin in/out/up/down.

5.6. Oil based formulation.

- of caporesc. Syrup / Caporesc. veg. oil Suspn.
- useful for taste masking.

J Wilson.
August '85.